REMARKS

Prior to the present amendment, claims 17-59, 67, 68, 70-73, 76-80 and 82-86 were pending. Of the pending claims, claims 19, 21-59, 80, and 82-84 were withdrawn by the examiner as being drawn to non-elected inventions. By the present amendment, claims 17, 18, 20, 67, 68, 70-73, and 76-79 have been amended and new claim 87 has been added. Accordingly, claims 17, 18, 20, 67, 68, 70-73, 76-79, 85-87 are under consideration.

The Invention

The invention provides a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors. The claimed polypeptide contains a heavy chain variable region of a human antibody with factor VIII specificity, and a light chain variable region of a human antibody.

Claims 17-18, 67, 68, 70-73, and 76-79 are directed to the polypeptide. Claim 20 relates to a pharmaceutical composition containing the polypeptide with a pharmaceutically acceptable carrier. Claims 85 and 86 provide a method for producing the polypeptide.

Rejection under 35 U.S.C. §101

In the Office Action, claims 17, 20, 67-68, 70-73, and 76-79 were rejected under 35 USC §101. According to the examiner, the claimed invention is directed to non-statutory subject matter. The examiner states that the claims as written do not sufficiently distinguish over polypeptides as they exist naturally. The examiner suggested that the claims be amended by inserting the word "isolated," as disclosed on page 5, lines 23-24 of the specification.

Applicants have amended the claims by inserting the word "isolated" as suggested by the examiner. As correctly indicated by the examiner, support for the word "isolated"

is found in the specification as originally filed, *inter alia*, page 5, lines 23-24. Accordingly, the rejection of the claims under 35 U.S.C. §101 is now moot and should be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 18 and 20 were rejected under 35 U.S.C §112, second paragraph for allegedly being indefinite. The examiner states that it is improper to recite "A" composition in claim 18. The examiner suggested replacing the word "A" with the word "The."

Applicants have amended claim 18 in accordance with the examiner suggestion. Therefore, the rejection of claim 18 under 35 U.S.C. §112, second paragraph is now moot and should be withdrawn.

The examiner did not provide an explanation for the rejection of claim 20 under 35 U.S.C. §112, second paragraph. Claim 20 appears to be in compliance with 35 U.S.C. §112. Accordingly, applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §102(b) over Davies et al.

Claims 17, 18, 70-73, 76-79 and 85-86 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Davies (Davies et al., 1997, *Thromb. Haemostas.* Supplement: 2352). The examiner states that Davies et al. teaches eight human factor VIII (FVIII) specific scFvs selected by panning on immobilized rFVIII. According to the examiner, Davies et al. further teaches the method of producing recombinant scFv's specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies. Thus, the examiner contends that the polypeptides of Davies et al. are the same as the claimed polypeptides capable of specifically binding to FVIII and interference with FVIII inhibitors.

Applicants respectfully disagree. Davies et al. discloses the selection of eight FVIII specific scFvs by panning on immobilized rFVIII. Davies et al. report that the VH domains of three of the scFvs are encoded by the V_H3 family genes V3-15+, DP38 and DP54, two are encoded by the V_H5 family, and the remaining three by the DP74 gene of the V_H6 family. Similar information is given in Davies et al. for the VL domains.

As mentioned in the previous response, Davies et al. discloses FVIII specific scFvs. The polypeptides of the claimed invention bind to FVIII and interfere with the activity of FVIII inhibitors. Davies et al., however, is completely silent about whether the scFvs are capable of interfering with the activity of FVIII inhibitors.

In response, the examiner contends that interference with the activity of FVIII inhibitors is considered to be an inherent property of the scFv polypeptides disclosed in Davies et al. Applicants respectfully disagree.

Contrary to the examiner's assertion, scFvs that specifically bind FVIII and interfere with the activity of FVIII inhibitors is neither disclosed or suggested, nor an inherent property of the scFvs of Davies et al. Davies et al. examined the Ig variable domain structure of immune FVIII antibodies obtained by V gene phage display technology from Haemophilia A patients with high peak inhibitor levels. The expectation of any skilled person is that the approach of Davies et al. would yield scFvs which strongly inhibit FVIII.

Pivotal to the present invention is the novel and surprising discovery of scFvs that specifically bind FVIII and interfere with the activity of FVIII inhibitors. The claimed polypeptides typically use different VH segments than those of the scFvs disclosed in Davies et al. For example, the VH segments used in the claimed polypeptides include C2 domain (DP10, DP14, DP88), A3-C1 domain (DP15, DP31, DP49, DP77), and A2 domain (DP10, DP47). In contrast, the VH segments used in the scFVs of Davies et al. are V3-15+, DP38, DP54, DP73, DP74.

The differences in the VH segments used in the claimed polypeptides and those used in the scFvs of Davies et al. make it unlikely that the scFvs described in Davies et al. possess the claimed features of (i) specific binding to FVIII and (ii) interference with FVIII inhibitors.

As correctly noted by the examiner, "a chemical composition and its properties are inseparable." The examiner implies that chemical compositions that are the same have the same properties. A corollary of this principle is also true. Chemical compositions that are not the same are expected not to have the same property.

As mentioned above, the VH segments used in Davies et al. differ from those of the polypeptides of the claimed invention. The difference allows a skilled person to draw the conclusion that the scFvs of Davies et al. differ from those of the present invention. Thus, the properties of the scFvs of Davies et al. and the properties of the claimed polypeptides are also expected to differ. Therefore, the ability to interfere with FVIII inhibitors cannot be said to be an inherent property of the scFvs disclosed in Davies et al.

In fact, not all svFvs that bind FVIII are capable of interference with FVIII inhibitors. Applicants provide herewith a Rule 132 Declaration executed by Dr. Johannes Jacobus Voorberg, a co-inventor of the claimed invention.

In the Rule 132 Declaration, Dr. Voorberg provides an experiment which demonstrates that not all scFvs that bind FVIII are capable of interference with FVIII inhibitors. Therefore, interference with FVIII inhibitors is **not** an inherent property of all scFvs that bind FVIII.

Therefore, the examiner is incorrect to conclude that the ability to interfere with FVIII inhibitors is an inherent property of the scFvs of Davies et al.

Further, as mentioned in the previous response (see page 16 of the January 14, 2005 Amendment), Davies et al. does not provide an enabling disclosure. In response, the examiner states in the Office Action that "a reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of the invention. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention."

There is no indication that the scFvs of Davies et al. were deposited with any depository institution to provide access to the public. Thus, the public is not in possession of the eight scFvs disclosed in Davies et al. Therefore, the disclosure of Davies et al. is not described in a way which would have allowed one skilled in the art to make the scFvs disclosed. Moreover, the disclosure of Davies et al. is not sufficient to fully characterize the structure of the scFvs. Accordingly, the disclosure of Davies et al. is not enabling.

The present invention is not described by Davies et al., nor was it in the public domain. There is nothing in Davies et al. or in the public domain which would disclose to a skilled person to make and select scFvs as claimed in the present invention.

Accordingly, the claimed invention can not be considered to be anticipated by Davies et al. Therefore, applicants respectfully request that the rejection of the claims over Davies et al. under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Rejection under 35 U.S.C §103(a) over Davies et al. in view of U.S. Patent No. 4,731,245

Claim 20 was rejected under 35 U.S.C. §103(a) for allegedly being obvious over Davies et al. in view of U.S. Patent No. 4,731,245 (the '245 patent). The examiner's summary of the Davies et al. reference with respect to the §103(a) rejection is similar to that described above with respect to the §102(b) rejection.

Claim 20 is directed to a pharmaceutical composition comprising the polypeptide according to claims 17 or 18 with a pharmaceutically acceptable carrier. The examiner concedes that Davies et al. does not disclose a pharmaceutically acceptable carrier.

To rectify the deficiency, the examiner cites the `245 patent for disclosing a composition comprising an antibody with a pharmaceutically acceptable carrier. Therefore, the examiner concludes that it would have been *prima facie* obvious to formulate the antibody fragments disclosed in Davies et al. in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent.

Applicants respectfully disagree. As mentioned above, there is no disclosure or suggestion in Davies et al. of polypeptides that bind to FVIII and interfere with the activity of FVIII inhibitors. Therefore, claim 20 is patentable over Davies et al. at least for the same reasons that claims 17 and 18 are patentable.

Even if it was proper to combine Davies et al. and the `245 patent, the combination does not result in the claimed invention. As discussed, Davies et al. does not disclose or suggest scFvs that bind to FVIII and interfere with the activity of FVIII inhibitors. Thus, the combination of Davies et al. and the `245 patent does not disclose or suggest a pharmaceutical composition comprising a polypeptide that binds specifically to FVIII and interfere with the activity of FVIII inhibitors.

Accordingly, applicants respectfully request that the rejection of claim 20 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Rejection under 35 USC §103(a) over Davies et al. in view of Foung et al. and U.S. Patent No. 5,916,771

Claims 17 and 67-68 were rejected under 35 U.S.C. §103(a) over Davies et al. in view of Foung et al., 1986, Chapter 13 in Methods in Enzymology, Vol. 12, pages 168-

174 and U.S. Patent No. 5,916,771 (the `771 patent). The examiner's summary of the Davies et al. reference with respect to the §103(a) rejection is similar to that described above with respect to the §102(b) rejection.

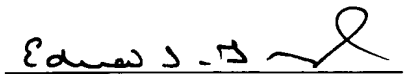
The examiner acknowledges the failure of Davies et al. to disclose that the human antibody is an IgG (as recited in claim 67) from subclass IgG4 (as recited in claim 68). To rectify the deficiency, the examiner cites Foung et al. for its disclosure of the generation of human monoclonal antibodies, and the `771 patent for disclosing IgG4 antibodies. Thus, the examiner concludes that the invention is *prima facie* obvious.

Applicants respectfully disagree. As stated above, nowhere in Davies et al. is there any disclosure or suggestion of a polypeptide that is capable of binding to FVIII and interferes with the activity of FVIII inhibitors. The secondary references, namely Foung et al. and the `771 patent, also do not disclose or suggest such polypeptide. The rejection of the claims is improper in the absence of such a disclosure or suggestion. Therefore, the claimed invention cannot be considered obvious over Davies et al. in view of Foung et al. and the `771 patent.

Accordingly, applicants respectfully request that the rejection of claims 17, 67-68 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

For the reasons given above, allowance of the pending claims is earnestly requested. If the examiner has any questions regarding this amendment, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Edna I. Gergel, Ph.D.
Registration No. 50,819
Agent for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791-4407
Tel. (516) 822-3550
Fax. (516) 822-3582
206239_1